EPA
United States
Environmental Protection
Agency

Cancer Risk Assessment for Environmental Chemical Mixtures and Combined Chemical and Nonchemical Stressors

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Outline

1. Cancer Risk Assessment at EPA: Brief Overview
2. Component Methods for Cancer Assessment of Chemical Mixtures

Risk Assessment

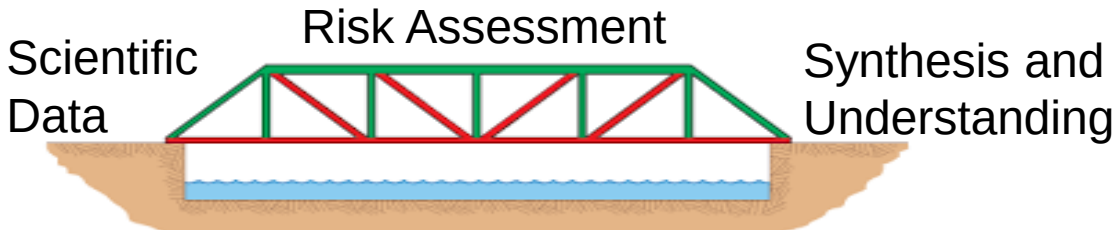
Systematic analysis, determine existence and extent of hazards to human health (outcome & magnitude), given available data

Cancer risk assessments inform decision-makers;
Goals of cancer risk assessments can vary over a range:

- understand whether a chemical has potential to increase human cancer incidence either alone or in combination
- quantify the relationship between dose, or more generally human exposure, and probability of induction of a carcinogenic effect

EPA decision-making typically informed by single chemical risk assessments

- Follow EPA statutes and guidelines



Sources: Society of Risk Analysis. Definitions
National Research Council. 1983. Risk assessment in the federal government. Managing the process. National Academy Press, Washington, DC

Cancer Assessment for Chemicals at EPA: Overview

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Human Epidemiological Data
Animal Bioassay Data
Supporting Data
- short-term tests of genotoxicity and other relevant properties
- pharmacokinetic & metabolic studies
- mechanistic studies
- SAR studies

Hazard Identification

Does chemical have potential to increase human cancer incidence either alone or in combination?
Weight of Evidence (WOE)

Human Epidemiological Data
Animal Bioassay Data
Supporting Data

Dose-Response Assessment

- **Conduct dose-response modeling**
- **Identify critical effect**
- **Identify point of departure (POD)**

POD
Supporting Data

Calculate Risk Values

- **Oral slope factors**
- **Inhalation unit risk**

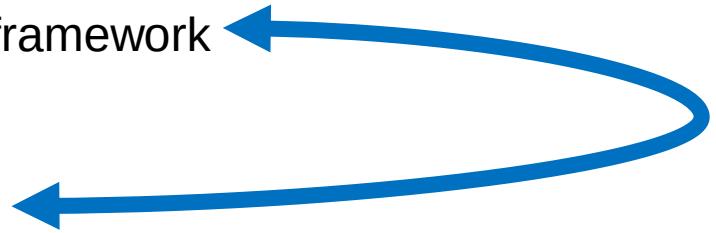
EPA Hazard Identification for Carcinogenic Effects

United States Environmental Protection Agency

- Integrates information to characterize weight-of-evidence (WOE) regarding chemical's carcinogenic potential in humans by exposure route
  - Narrative
  - 5 Categories (Carcinogenic, Likely to be carcinogenic, Suggestive…)

- Opportunities to improve organization and analysis of mechanistic info
  Mode of action (MOA) framework
  Adverse outcome pathway (AOP) framework

  Hallmarks of Cancer
  Key Characteristics of Cancer



For data-rich chemicals (e.g., epi, bioassay), mechanistic info fill data gaps; For data-poor chemicals, mechanistic info could be basis of hazard identification, with caveats

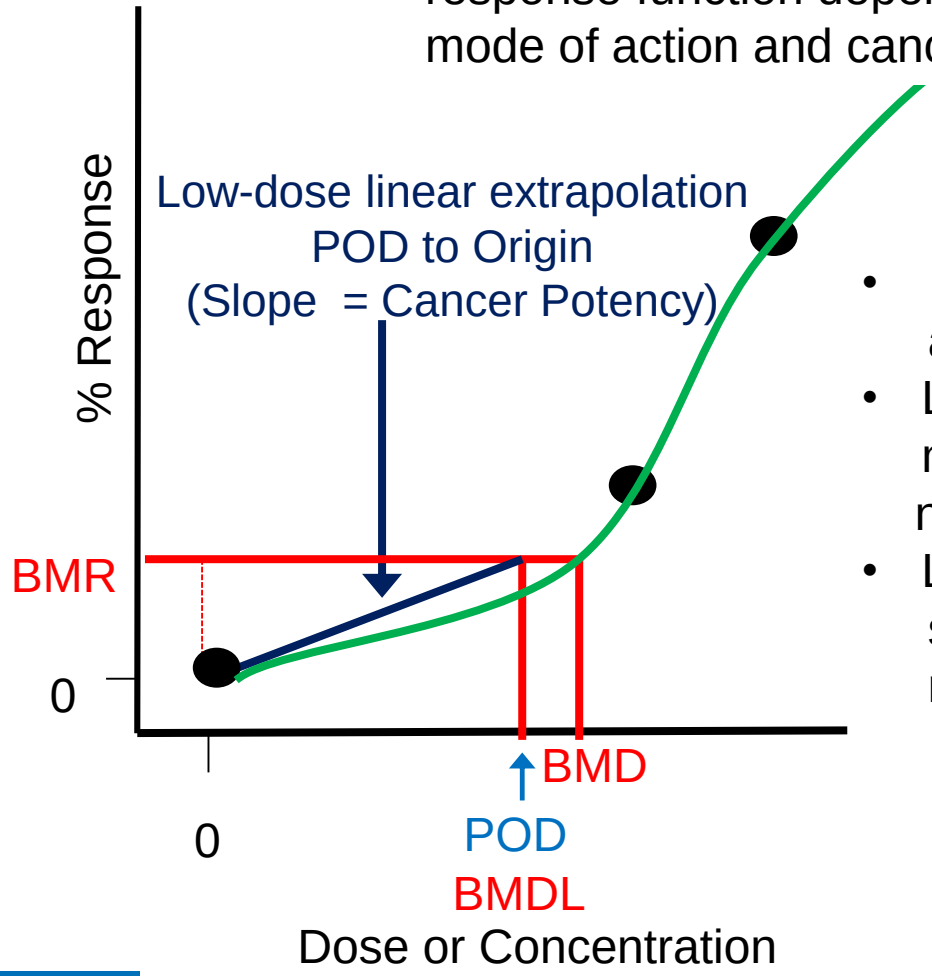
  - An increased understanding of relationship between activities in a NAM assay and adverse outcome in vivo increases confidence in the predictivity of mechanistic info

US EPA 2005 Guidelines for Carcinogen Risk Assessment; Smith et al., 2016; Dean et al., 2017 Guyton et al 2018

EPA Approaches: Cancer Dose-response Assessment

EPA United States Environmental Protection Agency

EPA Cancer Guidelines: developing a chemical's cancer dose-response function depends on what is known about carcinogenic mode of action and cancer dose-response curve shape



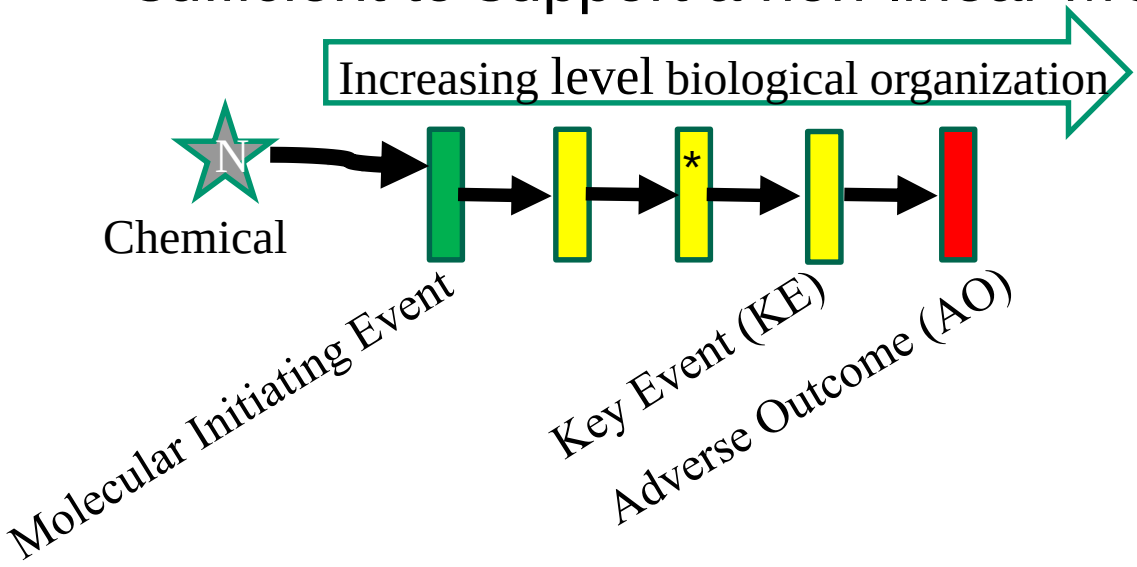
- Assume linear approach when MOA is anticipated to be linear (e.g., DNA reactivity)
- Linear approach used if there are mixed modes of action (e.g., genotoxic and non-genotoxic)
- Linear approach used as a matter of science policy if carcinogenic MOA is not well understood

BMD	Benchmark Dose
BMDL	Lower 95% confidence interval on BMD
BMR	Benchmark Response
POD	Point of Departure

EPA. 1986. Guidelines for Carcinogen Risk Assessment. 51 FR 33992-34003
EPA. 2005. Guidelines for Carcinogen Risk Assessment. 70 FR 17765-17817

EPA Approaches: Cancer Dose-response Assessment (2)

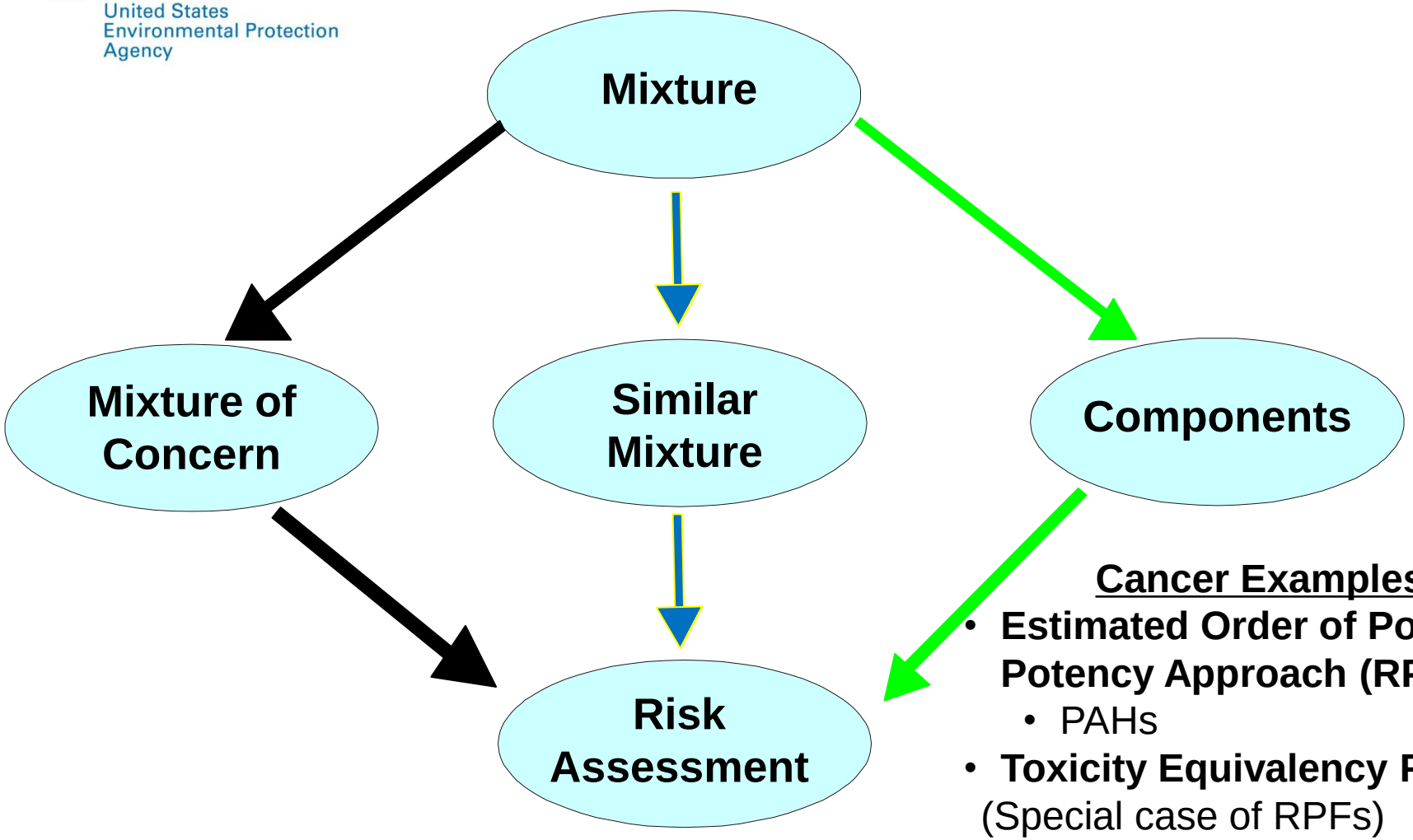
- Nonlinear approach appropriate when evidence sufficient to support a non-linear MOA



- If, in a well understood MOA, a KE does not occur below a certain dose, potential candidate for nonlinear approach
- EPA Chloroform Cancer Assessment
  Unlikely genotoxic MOA; strong evidence carcinogenic responses in bioassays associated with cell death/regenerative hyperplasia
- Nonlinear appropriate
- Chloroform RfD (based on a non-cancer endpoint) protective against increased risk of cancer

EPA. 2001. Toxicological Review of Chloroform

Mixture Approaches: Examples



Cancer Examples

- **Estimated Order of Potential Potency Approach (RPF)**
  - PAHs
- **Toxicity Equivalency Factor** (Special case of RPFs)
  - Dioxin-like Compounds
- **Response Addition**
  - Superfund Site Mixtures

US EPA, 1989; 1993; 2000; 2010; van den Berg et al., 2006

KEY CONCEPT: ADDITIVE JOINT TOXIC ACTION OF MIXTURE COMPONENTS

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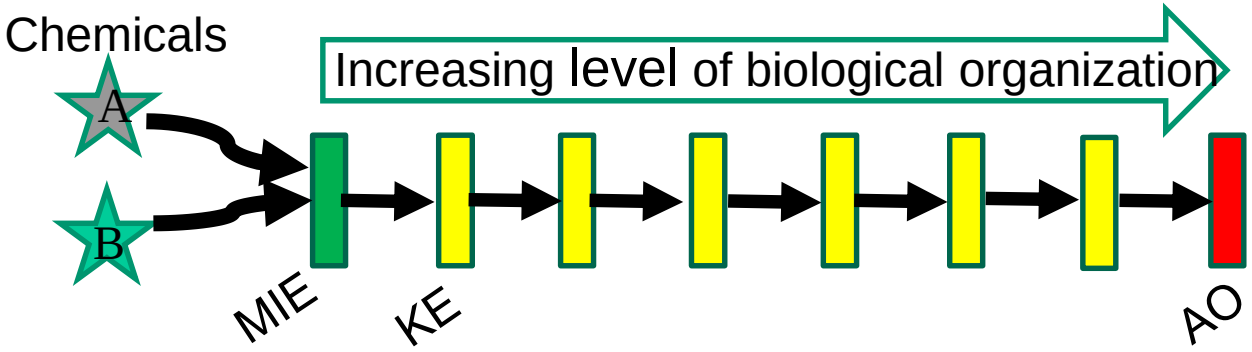
- Simple similar action
- Dose addition—toxicity equivalence factors (TEFs), relative potency factors (RPFs)
  - Addition of component doses, scaled for relative toxicity
  - Assumes components affect same pathway of toxicity



Simple Case: Mixture of 2 chemicals, act as toxicodynamic clones, affect same adverse outcome thru same mode of action; doses add at MIE

MIE Molecular Initiating Event
KE Key Event
AO Adverse Outcome

Adapted from US EPA (2017) Adverse Outcome Pathway (AOP) Factsheet
https://www.epa.gov/sites/production/files/2017-03/documents/aop_research_brief_03_2017.pdf

Dose Addition Method using Relative Potency Factors (RPFs)

For mixture components, chemical i and index chemical, the RPF_i may be estimated as the ratio of equally toxic doses of the 2 chemicals

$$RPF_i = \frac{ED_X\left(Index\ Chemical\right)}{ED_X\left(Chemical_i\right)}$$

ED_x "Effective Dose" at which x% response is observed.

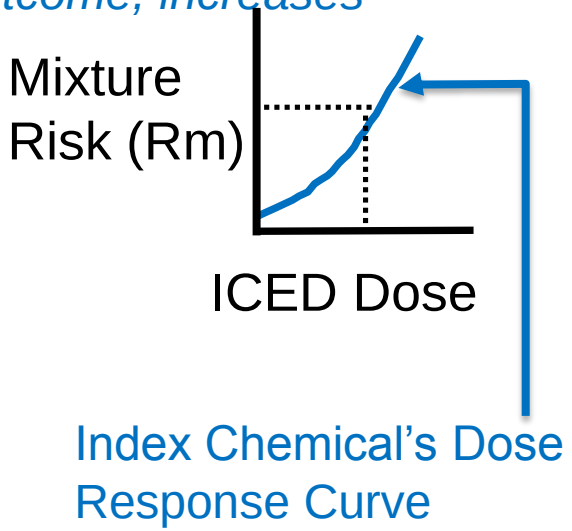
Potency measures can be based on animal bioassay data or other data (e.g., NAM data). If based on other data, increased understanding of relationship between measured activity and adverse outcome, increases confidence in RPF.

$$Rm = f_1(D_1 + RPF_2D_2 + RPF_3D_3\ldots) = f_1(ICED)$$

where

RPF_i Scales potency of chemicals 2 and 3 relative that of index chemical

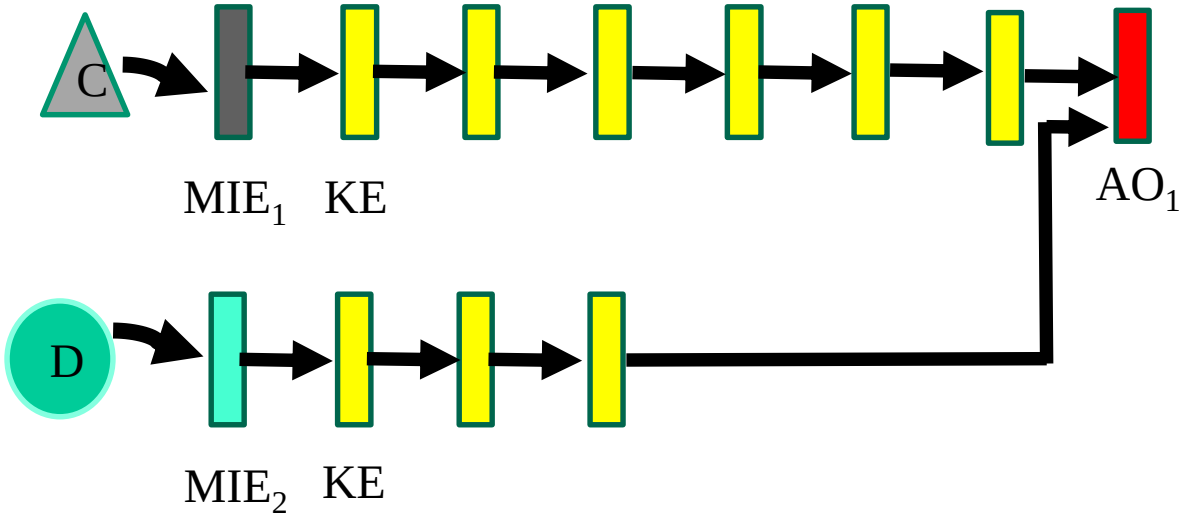
ICED Index chemical equivalent dose



US EPA, 2000

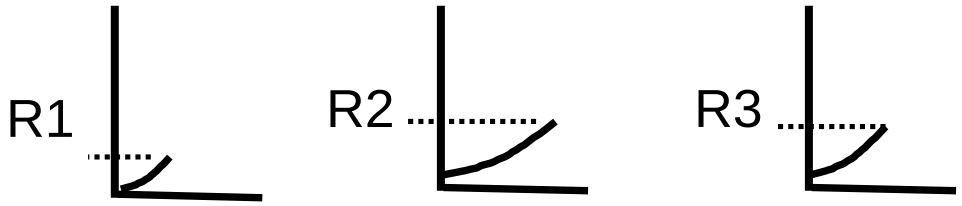
KEY CONCEPT: ADDITIVE JOINT TOXIC ACTION OF MIXTURE COMPONENTS

- Simple dissimilar action
  - Response addition—cancer risk sums
    - Addition of component risks
    - Assumes toxicological and statistical independence
    - Generally applied when it is established that chemicals are toxicologically dissimilar



Mixture of 2 toxicologically independent chemicals affect same adverse outcome thru different pathways

Response Addition: Applied Extensively to Estimate Mixture Risk (Rm) for Carcinogens

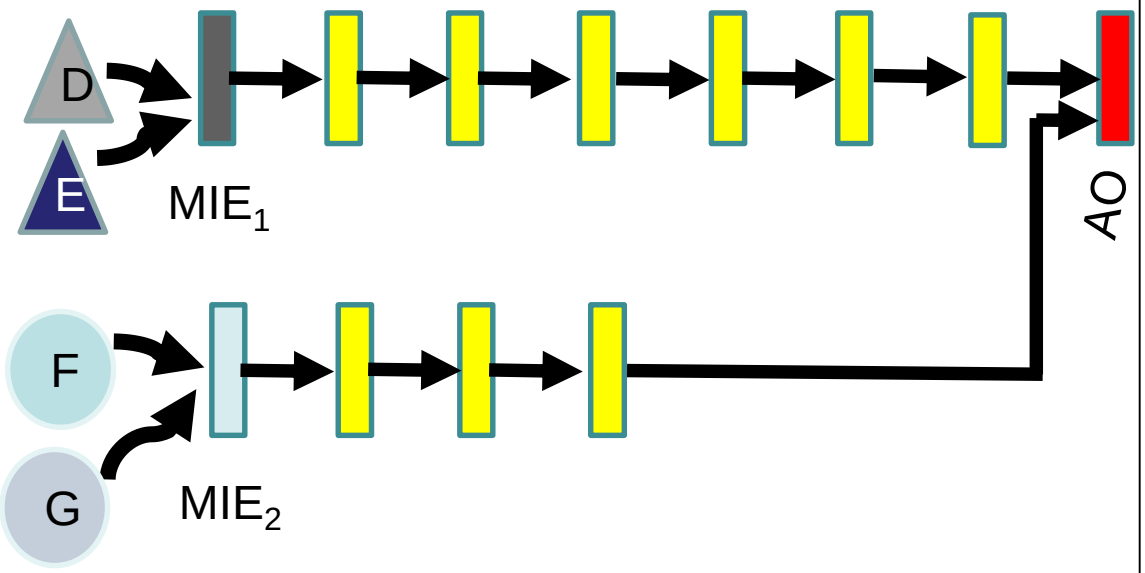


Response Addition: Independence of Toxic Action and Statistical Independence

$$Rm = f_1(D_1) + f_2(D_2) + f_3(D_3) = R_1 + R_2 + R_3$$

For a common health outcome, the toxicity caused by the first chemical has no impact on the toxicity caused by the second chemical.

Integrated Addition Model

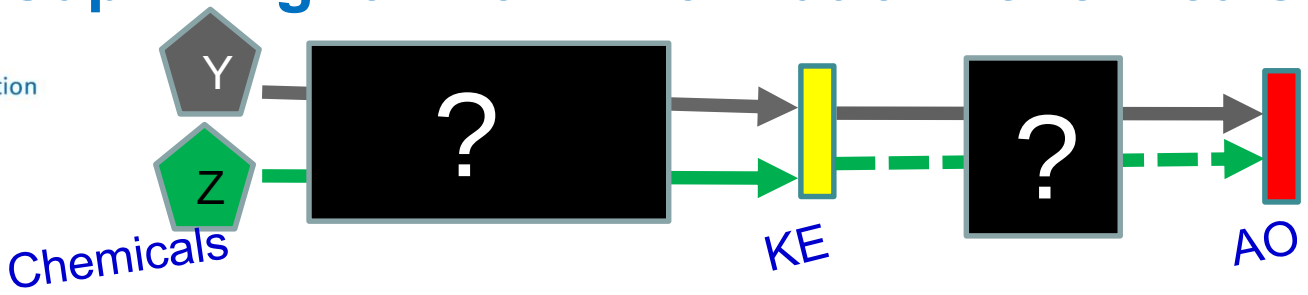


- Chemicals D & E and Chemicals F & G affect an adverse outcome (AO) through 2 different molecular initiating events.
- Key Event Relationships linking AO to MIE_2 do not intersect the key event relationships linking AO to MIE_1.

- Many mixture exposures include component chemicals that do not fall neatly into the same toxicological similarity group.
- Hybrid approach incorporates both *dose addition* (D & E and F & G 2 dose additive groups), and *response addition* (assumed across dose additive groups) yielding probabilistic risk estimate of dichotomous endpoint.
- This approach has not been used in regulatory efforts; may be useful given messy nature of interactions between biological systems and anthropogenic chemicals, and for evaluating risks of complex mixtures.

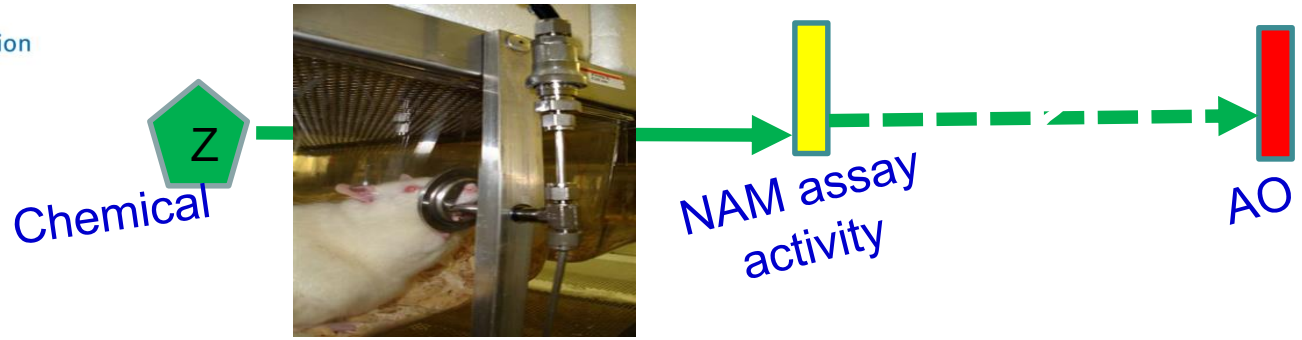
US EPA, 2003

Gap filling for “low information" chemicals



- Limited toxicodynamic info for a mixture of 2 chemicals; both perturb the same key event/s possibly upstream of adverse outcome (phenotypic anchor- chem Y)
- NAM data advantages : quicker/cheaper/offer additional insights into biological responses to chemical (other stressor) insults, relative to legacy test systems
- Opportunity in cancer assessment for NAM data to inform:
  - Mode of Action
  - Weight of Evidence
  - Low Dose Extrapolation
- Opportunity in mixtures assessment include:
  - Judge whether chemicals should be placed in a dose additive group
  - Estimate RPFs
  - Evaluate dose or response addition predictions at refined levels
  - Develop biologically-based models

Gap filling for “low information" chemicals (2)



- Concerns for informativeness/relevance of NAM data
- Different types of uncertainty
  - Assay Relevance: Is the activity being measured associated with a chemical exposure (relevance of the measure to the biology following exposure) and is it predictive of the endpoint of concern in the system?
  - External Generalization: Applicability of model system to endpoint in humans? E.g., lack of metabolism, dose issues, extrapolating animal model
- Context: Uncertainty of NAM data relative to that associated with legacy tests and measures (i.e., interpretation of existing data from current chemical toxicology testing strategies)
  - How “predictive” are our legacy tests and measures?
    - Mode of Action
    - Weight of Evidence
    - Low Dose Extrapolation

Conclusions

1. Cancer risk assessment of environmental chemical mixtures is critical to protect human health
2. Best evidence supporting mixture cancer assessments often obtained from epidemiological studies
   - Epi studies are resource intensive; but can evaluate chemical mixtures in relevant exposure range, mixing ratios, exposure routes, and species
3. Toxicological evidence potentially important source of mechanistic information for multiple stressors and cancer slope estimates
   - Often basis of component analyses
4. Opportunities thru “NAM” data to better inform cancer assessments
   - Hazard identification
   - Kinetic analyses
   - Mode of action analyses
   - Eventually, inform quantitative risk estimates
5. Opportunities thru NAM data to better inform component methods (e.g., common MOA group decisions, potentially measures of relative potency)
6. Cumulative assessments of disparate stressors, a significant challenge. Can consider such risks using a whole mixture perspective, exploratory research needed for understanding risks associated (and underlying interactions among) with combined exposures.

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